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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 05/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/810,165	YOUNG ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *23-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22 and 33-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/29/05; 9/29/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I in the reply filed on March 1, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-40 are all the pending claims for this application.

Claims 1-22 and 33-40 are all the claims under examination. Claims 23-32 are withdrawn from consideration as being drawn to non-elected subject matter.

Information Disclosure Statement

2. The U.S. patent, foreign patent documents and nonpatent literature references from the IDS' of June 29, 2005 and September 29, 2005 have been considered and made of record.

Specification

3. Applicant should amend the cross-reference of the instant specification to indicate that application no. 09/727,361 is now USPN 6,657,048, and that application no. 09/415,278 is now USPN 6,180,357.

4. All of the pages have an attorney docket number and name of the agent of record at the bottom of the page.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-22 and 33-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-11 and 12-22 are indefinite for reciting "produced in accordance with a method", because it is not clear what "method" is being claimed.

b. Claims 2-11 and 13-22 are indefinite for reciting "in accordance" with respect to their corresponding independent claims, claims 1 and claims 12, respectively, because it is unclear if the phrase means a similar method or a method with similar properties or a method with similar steps.

c. Claims 11 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: What steps are needed to produce the individually customized anti-cancer antibodies and what steps determine that they are individually customized, in claims 1 and 12, respectively?

d. The term "essentially" in the phrase "essentially benign to non-cancerous cells" of claims 1 and 12, is a relative term, which renders the claims indefinite. The term "essentially" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Do the antibodies have any

cytotoxic effects on non-cancerous cells, and if so, what cell types, organs or tissues are affected and to what extent does this occur?

e. Claims 7 and 18 are indefinite for reciting "mediated through catalyzing the hydrolysis of cellular chemical bonds" because the exact meaning of the phrase is not clear. It is not clear what cellular chemical bonds are being hydrolyzed or if the antibody catalyzes the reaction or if the antibody causes a cascade effect that causes the hydrolysis.

f. Claims 8 and 19 are indefinite for reciting "is mediated through producing an immune response against putative cancer antigens" because the exact meaning of the phrase is not clear. Does the antibody cause an immune response or does the antibody trigger a cascade effect that causes an immune response? What are "putative cancer antigens"? Are the antigens known in the art, known to be expressed on cancer cells, or is the immune response generated from this method intended to be cross-reactive for as yet to be defined cancer cell antigens?

g. Claims 9 and 20 are indefinite for reciting "mediated through targeting of cell membrane proteins" because the exact meaning of the phrase is not clear. Does the antibody bind to the cell membrane protein and cause cytotoxicity or does the antibody trigger a cascade effect that causes cytotoxicity that in turns interferes with the function of the protein?

h. Claims 10 and 21 are indefinite for reciting "mediated through production of a conformational change in a cellular protein" because the exact meaning of the phrase is not clear. Does the antibody cause a conformational change or does the antibody act

like an enzyme and produce a reaction that causes a change in the protein such as a substrate producing a product or does the antibody cause a cascade effect that causes the conformational change?

i. Claims 1, 12 and 33 are indefinite in the recitation "monoclonal antibody encoded by a clone deposited with the ATCC as PTA-4621" in claims 1, 12 and 33. The specification at pg. 30, lines 3-8 discloses that the clone deposited with the ATCC as PTA-4621 is the hybridoma cell line H460-16-2, which produces monoclonal antibody H460-16-2. The art teaches that a hybridoma is produced by the fusion between a B cell and a myeloma cell, which is a cancer cell that provides the resultant B cell-myeloma hybrid, or hybridoma, with the capacity to proliferate indefinitely (see Campbell et al, Biology, 5th ed. pg. 856, 1999). Thus, when read in light of the specification and in view of the knowledge in the art, one of ordinary skill in the art would not be reasonably apprised of the metes and bonds of "a monoclonal antibody encoded by a clone deposited with the ATCC as PTA-4621" as presently claimed because a hybridoma secretes or produces mouse antibodies of a single idiotype (i.e., the monoclonal antibodies produced from a given hybridoma are identical). Further, it is unclear if the claims are directed towards the hybridoma deposited with the ATCC as PTA-4621 or is some clone that is genetically engineered such that other forms of monoclonal antibodies including chimeric and humanized monoclonal antibodies are "encoded" by the clone PTA-4621. It is unclear what is contemplated by the phrase "monoclonal antibody encoded by a clone deposited with the ATCC as PTA-4621" and

one of skill in the art could not determine the metes and bounds of the claimed invention as written. See the Examiner's further comments under section 6, infra.

Amending claims 1, 12 and 33 to recite "the monoclonal antibody produced by the hybridoma deposited with the ATCC as PTA-4621" would overcome this rejection, provided no new matter is introduced.

j. Claim 33 is indefinite for reciting "extending survival and delaying disease progression" because the exact meaning of the phrase is not clear. What is the time period for delay, what is meant by "progression", does the method reduce or prevent tumor growth or metastases, and how is this measured?

k. Claims 1-11 and 33-40 are indefinite in the recitation of "having the identifying characteristics of a monoclonal antibody encoded by a clone deposited with the ATCC as PTA-4621" in independent claims 1 and 33 because the exact meaning of the phrase is not known. The properties or characteristics that are shared by the claimed monoclonal antibodies and the monoclonal antibody produced by clone PTA-4621 are not clearly defined by the claims and the specification does not provide a standard for ascertaining the requisite degree or nature of the identifying characteristic(s). Does the phrase "having the identifying characteristics of a monoclonal antibody encoded by a clone deposited with the ATCC as PTA-4621" mean that the antibody has the same antigen specificity, epitope specificity, same heavy and light chain sequences, internalization, immunogenicity, tumor growth inhibitory property, cytotoxic property, ability to mediate antibody-dependent cellular cytotoxicity (ADCC) or activate cellular-dependent cytotoxicity (CDC) or is/are some other identifying characteristic(s)

contemplated by the phrase? Further, is the monoclonal antibody which binds the CD44 antigenic moiety the same antibody that has the identifying characteristics of a monoclonal antibody encoded by a clone deposited with the ATCC as PTA-4621 or is the antibody that has the identifying characteristics of the deposited monoclonal antibody used to limit the CD44 antigenic moiety and what is the relationship with the claimed anti-CD44 monoclonal antibody as well as the monoclonal antibody encoded by a clone deposited with the ATCC as PTA-4621? As written, one or ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention and a competitor could not determine whether or not they are infringing.

Biological Deposit

6. The examiner acknowledges that the claims require the monoclonal antibody deposited with the ATCC as accession number PTA-4621 and would form the basis for a rejection under 35 U.S.C 112, first paragraph (enablement), however, it is noted that Applicant has completed the requirements for the deposit of biological materials, i.e., the specification at page 39 discloses that the hybridoma cell line H460-16-2 was deposited in accordance the Budapest Treaty, with American Type Culture Collection (ATCC), 10801 university Blvd., Manassas, VA 20110-2209 on September 4, 2002, under accession no. PTA-4621, and that depositors assure that *all restrictions imposed on the availability to the public of the deposited materials will be irrevocably removed upon granting a patent.*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-22 and 33-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a) anti-cancer antibodies which bind antigen and comprise an Fc region, wherein the antibodies are cytotoxic to cancerous cells and essentially benign to non-cancerous cells, wherein the cytotoxicity is through antibody dependent cellular toxicity, complement dependent cellular toxicity, producing an immune response against a cancer antigen, targeting of proteins, wherein the method of production utilizes tissue of cancerous and non-cancerous cells, and wherein the antibodies are those species recited in the claims recognizing the same antigen (i.e., "CD 44 antigenic moiety"; p. 23, line 8) as the antibody (H460-16-2) of the hybridoma, PTA-4621, or being the H460-16-2 antibody of the hybridoma, PTA-4621, upon successful completion of the biological deposit, b) a method of treating breast or prostate cancer or melanoma in a patient with administering the H460-16-2 antibodies or antibodies recognizing the CD 44 antigenic moiety, wherein the antibodies are cytotoxic to cancerous cells and essentially benign to non-cancerous cells, wherein the cytotoxicity is through antibody dependent cellular toxicity, complement dependent cellular toxicity, producing an immune response against a cancer antigen, targeting of proteins, wherein the method of production utilizes tissue of cancerous and non-cancerous cells, and c) a method of reducing breast and prostate cancer tumor burden in a patient administering the H460-16-2 antibodies, **does not reasonably provide**

enablement for a) the anticancer antibody fragments, or any anticancer antibody that mediates cytotoxicity through catalyzing the hydrolysis of any cellular chemical bond or through production of a conformational change in a protein, wherein the fragments recognize the same antigen as an antibody having the identifying characteristics of a monoclonal antibody encoded by a clone deposited with the ATCC as PTA-4621 or b) any method of treatment in a patient with any of the anticancer antibodies having the identifying characteristics of a monoclonal antibody encoded by a clone deposited with the ATCC as PTA-4621 that is produced by any method for individual customized antibodies directed against any cancer or any fragments of antibodies that would not bind antigen, c) any method of treating of any cancer that is mediated by catalyzing the hydrolysis of a chemical bond or mediated through a conformational change in a protein with anticancer antibodies having the identifying characteristics of a monoclonal antibody encoded by a clone deposited with the ATCC as PTA-4621, or d) any method of reducing the tumor burden for any tumor in a patient with administering antibodies having the identifying characteristics of a monoclonal antibody encoded by a clone deposited with the ATCC as PTA-4621 or being a monoclonal antibody encoded by a clone deposited with the ATCC as PTA-4621. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in

the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

A. Antibody fragments and catalytic antibodies are unpredictable in their binding properties.

The claims are broadly drawn to any fragments of antibodies having the identifying characteristics of a monoclonal antibody encoded by a clone deposited with the ATCC as PTA-4621 or being a monoclonal antibody encoded by a clone deposited with the ATCC as PTA-4621, such as a light chain, a heavy chain, an Fc region, etc, that alone would not bind antigen or be cytotoxic. The claims are broadly drawn to any CD 44 antigenic moiety antibody that catalyzes the hydrolysis of any chemical bond, i.e. is a catalytic antibody or causes a conformational change in a protein. The specification teaches production of anti cancer antibodies that are directed against breast cancer, melanoma and prostate cancer (see Tables 1 and 2). The specification teaches the antibodies are either cytotoxic or cytostatic (page 17, lines 2-3) and act through ADCC or CDC (see page 26). The specification fails to enable antibody fragments as broadly claimed which encompasses VH, VL, CH1, CH2, CH3, Fc, etc would not bind antigen or be cytotoxic or catalytic anti-cancer antibodies that catalyze the hydrolysis of a chemical bond or any antibody that acts through production of a conformational change in a protein.

The claims are not commensurate in scope with the enablement provided in the specification. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that fragments of antibodies as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an antibody, have the required binding function. The specification provides no direction or guidance regarding how to produce fragments of antibodies as broadly defined by the claims or what fragments, VH, VL, CH1, CH2, CH3, Fc, etc would be cytotoxic. Undue

experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Claims 7 and 18 are broadly drawn to antibodies that mediate through hydrolysis of any chemical bond which is broadly drawn to catalytic antibodies, however, the specification does not enable any catalytic antibodies. The specification does not teach any transition state analogs or methods to obtain such antibodies or if such antibodies are effective as anti-cancer antibodies. The specification does not teach the antigen to which the antibodies bind and as such one skill in the art could not synthesize a transition state analog for production of a catalytic antibody or an antibody that would hydrolyze a chemical bond. As taught by Kim et al (U.S.Patent 4,963,355) catalysis using catalytic antibodies are obtained by immunization with a hapten that is related to be similar to but distinct from the selected substrate of the reaction to be catalyzed (see column 2, lines 1-11) which is a transition state analog. Thus, without knowledge of the substrate or the exact reaction to catalyze, one skilled in the art would not know how to produce the catalytic antibodies.

Claims 10 and 21 encompass an antibody that produces a conformational change in a protein, however, the specification does not teach any antibody with such properties as broadly claimed. In addition, the specification does not teach how one skill in the art would produce or screen for such antibodies.

Therefore, in view of the broadly claimed invention, the lack of predictability in the art as evidenced by Rudikoff et al and Kim et al and lack of guidance in the specification with regard to producing catalytic anti-cancer antibodies or antibodies that cause a

conformational change in a protein, one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

B. Antibody-based immunotherapeutics is unpredictable in treating ***some*** cancers

The claims are broadly drawn to a method of treating a human patient, suffering from any cancerous disease by administering anticancer antibodies or fragments of antibodies having the identifying characteristics of a monoclonal antibody encoded by a clone deposited with the ATCC as PTA-4621 or being a monoclonal antibody encoded by a clone deposited with the ATCC as PTA-4621, which are produced by some method (not claimed) and which act through hydrolysis of a chemical bond which broadly reads on catalytic antibodies or a method with an antibody that mediates through a conformational change in a protein.

Applicant has demonstrated that the patient specific antibodies of the instant application can be used to target breast cancer and melanoma cells in vitro, and breast and prostate cancer cells in vivo. However, the claims broadly read upon the treatment of all types of cancer. As disclosed in Johnson et al (Cancer Treatment Review Vol 2 1-31 1975), Table 2, only certain types of agents can treat certain types of cancer and that the same compound is not effective in the treatment of all types of cancers.

In addition the specification does not enable treatment in humans. Chatterjee et al Cancer Immunol. Imunother., 1994, 75-82, state the art recognized experience that for any novel therapy, the transition for the laboratory to the clinic (animal experiments to the bedside) is a quantum leap (Cancer Immunol. Imunother., 1994, see Introduction). Results obtained under controlled conditions and in inbred animals often

differ from the clinical response obtained in patients. This applies to strategies drawn to cancer treatment.

The specification does not disclose whether the method is effective in patients with pre-existing tumors, and this is a significant omission in view of the well-known immunosuppressive effects of certain tumors. The criticality of a working example encompassing all of the method steps, especially the treatment of tumors, is underscored by Gura et al (Science Vol 278 11/97 1041-1042) in a discussion of potential shortcomings of extrapolating from in vitro studies and animal studies to similar procedures in cancer patients. Gura et al teaches that "xenograft tumors don't behave like naturally occurring tumors in humans" (page 1041, second col, second full paragraph) and that there were "gross difference in sensitivity in real tumors in mice and in the clonogenic assay" (page 1042, second col, second full paragraph). Further, Gura teaches that clonogenic assays "cannot tell researchers how anticancer drugs will act in the body" (page 1042, first-second col, bridging paragraph). One skilled in the art would reasonably conclude that evidence obtained in mouse xenograft models would not correlate with results expected in humans patients.

As evidenced by Seaver (1994; Genetic Engineering Vol 14(14):pages 10 and 21), selection of an antibody as an immunotherapeutic agent is an unpredictable task as the antibody must possess sufficient specificity and a high degree of affinity for its target for use as an immunotherapeutic agent and because these qualities are dependent on the physiology of the particular pathology and the accessibility of the target antigen. The specification is silent concerning what sort of specificity and affinity would be

necessary for the antibodies of the claimed treatment method so that one skilled in the art would not be able to practice the claimed invention without undue experimentation. In addition, the specification does not teach that antibodies produced in accordance with a method for production of individually customized anti-cancer antibodies, such as those listed in claims 12-15, can be used in any patient, including those from which the tumor cells were derived from.

Therefore, in view of the broadly claimed invention, the lack of predictability in the art as evidenced by Sever et al, Chatterjee et al, Gura et al, and Johnson et al, and lack of guidance in the specification, one of skill in the art would be required to perform undue experimentation in order to practice the claimed method inventions.

Priority

8. The later-filed application (i.e., the instant application) must be an application for a patent for an invention, which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application Nos. 10/603,2003; 09/727,361; and 09/415,278, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this

application. Prior application numbers 10/603,000, 09/727,361, and 09/415,278 do not provide adequate written support for the presently claimed subgenus of anti-CD44 antibodies interpreted as having the relevant identifying characteristics of the monoclonal antibody produced by the clone deposited with the ATCC as PTA-4621, which are not clearly set forth in the present claims as discussed under section 5.i), supra. The 10/647,818 application discloses that based on side-by-side comparison to the L178 Mab (anti-CD44 Mab; Becton Dickinson) with respect to the staining pattern, biodistribution and biochemical data, that the antigen recognized by H460-16-2 is one of the forms of CD44. Therefore, the effective filing date of claims 1-22 and 33-40 for purposes of applying prior art is deemed to be the filing date of the 10/647,818 application, i.e., 8/22/2003.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 1-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Tarin et al (US Patent 5,879,898; published 5/17/1995; hereinafter referred to as "Tarin I").

Claims 1-11 are being interpreted as drawn to a method for treating a patient suffering from a cancerous disease comprising administering to the patient anti-cancer antibodies binding to the antigen characterized as being bound to the H460-16-2 antibody of the hybridoma, PTA-4621, and produced by a method (not claimed) wherein the antibodies are cytotoxic, humanized and chimeric forms thereof, anticancer Mabs conjugated to a toxin, enzyme, radioactive compound to mediate treatment. Claims 5-10 are interpreted to mean that the antibody causes the effects through a cascade effect. Since the antibodies act through ADCC and CDC it is inherent that the antibodies mediate through an immune response (e.g., Fc pathway) and since the antibodies kill the cell it would be inherent that they would mediate through targeting cell membrane proteins, produce conformational changes in proteins, and hydrolyze chemical bonds upon killing the cell.

The method in which the antibodies were produced is immaterial to their patentability. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

Tarin I teaches that human CD44 expression is increased in various solid human tumors including breast, colon and bladder cancer and Tarin I teaches a method of mediating cytotoxicity of said tumor cells comprising administering a monoclonal antibody or antigen-binding fragment thereof (i.e., Fv, (Fv)2, Fab, Fab', F(ab)2) to a patient, wherein the monoclonal antibody is chimeric, humanized, or murine as well as conjugated to a toxin, chemotherapeutic, or radioactive label and mediates antibody-

dependent cellular cytotoxicity (ADCC) or activates complement-dependent cytotoxicity (CDC) (see entire document, particularly, columns 6-8, examples and Table 3). Thus, the administration of the CD44 specific monoclonal antibody or antigen-binding fragment thereof in human breast, colon and bladder cancer patients reads on contacting a human tumor cell that expresses CD44 because the antibody would necessarily bind CD44 expressed on the tumor cell surface. Further, due to the indefinite nature of the claims, the phrase "having the identifying characteristics of a monoclonal antibody encoded by a clone deposited with the ATCC as PTA-4621" is interpreted to mean that the claimed monoclonal antibody that binds CD44 (i.e., CD44 "antigenic moiety") has any of the following characteristics: mediates cytotoxicity, inhibits tumor growth (i.e., reduces tumor burden), specificity for CD44, mediates ADCC, and activates CDC, all identifying characteristics of the monoclonal antibodies taught by Tarin I as discussed above.

Thus, Tarin I anticipate the claims.

10. Claims 1-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Tarin et al (WO 94/12631, published 6/9/1994; hereinafter referred to as "Tarin II").

The claims and their interpretation have been described supra.

Tarin II teaches that human CD44 expression is increased in various solid human tumors including breast, colon and bladder cancer and Tarin II teaches a method of mediating cytotoxicity of said tumor cells comprising administering a monoclonal antibody or antigen-binding fragment thereof (i.e., Fv, (Fv)2, Fab, Fab', F(ab)2) to a patient, wherein the monoclonal antibody is chimeric, humanized, or murine as well as conjugated to a toxin, chemotherapeutic, or radioactive label and mediates antibody-dependent cellular cytotoxicity (ADCC) or activates complement-dependent cytotoxicity

(CDC) (see entire document, particularly, columns 6-8, examples and Table 3). Thus, the administration of the CD44 specific monoclonal antibody or antigen-binding fragment thereof in human breast, colon and bladder cancer patients reads on contacting a human tumor cell that expresses CD44 because the antibody would necessarily bind CD44 expressed on the tumor cell surface. Further, due to the indefinite nature of the claims, the phrase "having the identifying characteristics of a monoclonal antibody encoded by a clone deposited with the ATCC as PTA-4621" is interpreted to mean that the claimed monoclonal antibody that binds CD44 (i.e., CD44 "antigenic moiety") has any of the following characteristics: mediates cytotoxicity, inhibits tumor growth (i.e., reduces tumor burden), specificity for CD44, mediates ADCC, and activates CDC, all identifying characteristics of the monoclonal antibodies taught by Tarin II as discussed above.

Thus, Tarin II anticipate the claims.

11. Claims 33 and 36-40 are rejected under 35 U.S.C. 102(e) as being anticipated by Linderhofer et al. (US 20020051780; published May 2, 2002; hereinafter referred to as "Linderhofer").

Claims 33 and 36-40 are drawn to method for extending survival or delaying disease progression for a human tumor in a mammal by reducing the tumor burden, comprising administering monoclonal antibodies binding to an antigen characterized as being bound to the H460-16-2 antibody of the hybridoma, PTA-4621, and produced by a method (not claimed) wherein the antibodies are conjugated to a cytotoxic or radioisotope, the antibodies are murine, and humanized or chimeric forms thereof.

Claims 36 and 37 are interpreted to mean that the antibody causes the effects through through ADCC and CDC upon killing the cell.

Linderhofer discloses methods for the induction of an anti-tumor immunity by administering to a human or animal, a monoclonal anti-CD44 X anti-tumour -associated antigen antibody (¶0015; examples). The antibodies are able to induce tumour-reactive complement-binding antibodies and, thus, induce a humoral immune reaction (¶0015; 0078) and contribute directly to tumour killing via ADCC (¶0098); heterologous bispecific antibodies from mice and humans (¶0025-0055) and chimeric antibodies (¶ 0079) are disclosed. Linderhofer discloses that "long-lasting anti-tumour immunity" according to the invention is meant to be a period of time spanning at least several years. Further, due to the indefinite nature of the claims, the phrase "extending survival and delaying disease progression" is interpreted to mean that the immune response mediated by the anti-CD44 antibody produces a long-lasting anti-tumour immunity, all identifying characteristics of the monoclonal antibodies taught by Linderhofer as discussed above.

Thus, Linderhofer anticipate the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. Claims 1, 2, 5-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herrlich et al (US2002/0160010; published October 31, 2002; filed February 26, 1998; hereinafter referred to as "Herrlich") in view of Seth et al. (Proc. Nat'l. Acad. Sci. 88:7877-7881 (1991); hereinafter referred to as "Seth") or Galandrini et al. (J. Immunol. 153:4399-4407 (1994); hereinafter referred to as "Galandrini") and further in view of Denning et al. (Journal Immunol. 144:7-15 (1990); hereinafter referred to as "Denning" and as evidenced by the specification and the Becton Dickinson technical data sheet for L178 clone (published 11/5/03)).

The claims and their interpretation have been described supra. The specification teaches that the L178 Mab (Becton Dickinson) showed similar binding patterns seen with the inventive H460-16-2 Mab and that the L178 Mab identified proteins that were bound to H460-16-2 immunoprecipitates (p.22, lines 18-24).

Herrlich discloses anti-CD44 antibodies used in tumoral disease and immune processes in animals and humans comprising therapeutic treatment (¶0066; 0068; 0069) and humanized and chimeric forms of the antibodies (¶0058). The anti-CD44 Mab, L178, is disclosed for use in therapeutic methods, and is shown specifically, to

bind to CD44-expressing Langheran's and dendritic cells (Figure 1) and to mediate inhibitory effects in cell assays requiring Langheran's and dendritic cells (Figures 3-5). Herrlich does not disclose that the L178 Mab is cytotoxic and mediated anticancer effects through ADCC, through hydrolysis of cellular bonds, an immune response, by targeting cell membrane proteins, by production of a conformational change in a protein, and the antibodies are cytotoxic against cancerous cells and benign to non-cancerous cells.

Seth discloses that anti-CD44 Mabs can direct lysis by CTLs of specific cell targets through T-cell receptor independent pathways (Abstract; Figure 5) and Galandrini discloses that NK cell-mediated ADCC activity was enhanced with CD44 cross-linking with the J173 Mab (Figure 6). Galandrini teaches that:

> "The cytolytic process involves cytoskeleton organization. The CD44 intracytoplasmic domain binds to the cytoskeleton protein ankirin, and CD 44 ligations on T cells by hyaluronic acid affects ankirin polarization. Moreover, association of CD44 with cytoskeleton components is required for CD44-mediated functions. Consequently, the possibility that CD44 stimulates NK cyctotoxic activity by interfering with cytoskeleton reorientation and polarization must be considered." (p. 4406, Col. 2, ¶3).

Finally, Denning (cited on the Technical Data sheet for the L178 Mab of Becton Dickinson) discloses anti-CD44 Mabs mediating T-cell receptor independent T-cell activation (e.g., an immune response).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have used an anti-CD44 antibody such as L178 Mab in methods for treating a cancerous disease based on the binding characteristics that the Mab shares with the antibody of the claimed hybridoma, PTA-4621, and the

L178 Mab having all the biological properties of the antibody as claimed in view of Herrlich, Seth, Galandrini and Denning.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the methods of Herrlich to treat cancerous diseases using the L178 Mab because the clone was readily available at the time of the invention, and the CD44 antigen was well recognized as being expressed on T cells and could mediate an immune response (Denning), and as Seth and Galandrini disclose the use of CD44 Mabs for inducing ADCC and CDC with consequent effects on targeting cell membrane proteins, producing conformational changes in proteins, and hydrolyzing chemical bonds upon killing a tumor cell. Thus the claims were *prima facie* obvious at the time of the invention in view of the reference disclosures.

13. Claims 1 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herrlich et al (US2002/0160010; published October 31, 2002; filed February 26, 1998; hereinafter referred to as "Herrlich") in view of Seth et al. (Proc. Nat'l. Acad. Sci. 88:7877-7881 (1991); hereinafter referred to as "Seth") or Galandrini et al. (J. Immunol. 153:4399-4407 (1994); hereinafter referred to as "Galandrini") and further in view of Heider et al (6,372,441; published April 16, 2002; filed July 2, 1998; hereinafter referred to as "Heider") and Creekmore et al. (5,693,322; published December 2, 1997; filed March 11, 1993; hereinafter referred to as "Creekmore").

The claims and their interpretation are discussed supra.

Herrlich, Seth, Galandrini are discussed under section 8, supra. None of these references teach conjugating the anticancer cytotoxic Mab to a toxin, enzyme, radioactive compound or hematogenous cell and administering the antibody conjugate with a pharmaceutically acceptable adjuvant to mediate treatment.

Heider discloses for therapeutic applications, anti-CD44 specific antibody molecules linked to enzymes, toxins, and radioactive compounds (Col. 2, lines 28-31; Col. 3, lines 29-36). The antibody may also be linked to a cytokine or another immunomodulatory polypeptide, e.g. tumour necrosis factor or interleukin-2. Heider teaches formulations comprising the antibody molecules with suitable adjuvants. (Col. 4, lines 31-35).

Creekmore discloses methods of enhancing intercellular interaction between two or more cells through associational molecules targeted to the cellular surface comprising reacting a first associating antibody specific to an antigen on a first cell to the first cell under conditions wherein the first antibody binds to the first cell to form a first antibody-cell conjugate, reacting a second associating antibody specific to a second antigen on a second cell to the second cell under conditions wherein the second antibody binds to the second cell to form a second antibody-cell conjugate, and exposing the first antibody-cell conjugate to the second antibody-cell conjugate, wherein the first and second antibody-cell conjugates become non-covalently associated.(Col. 4, lines 32-44). Creekmore teaches hematogenous cells including granulocytes, B-cells, NK cells, T-cells, non-B and non-T lymphocytes, eosinophils and macrocytes/ macrophages (Col. 4, lines 55-64).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have used a cytotoxic anti-CD44 antibody such as L178 Mab in methods for treating a cancerous disease with the Mab being further conjugated to a toxin, enzyme, radioactive compound or hematogenous cell and administering the antibody conjugate with a pharmaceutically acceptable adjuvant to mediate treatment in view of Herrlich, Seth, Galandrini, Heider and Creekmore.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the methods of Herrlich to treat cancerous diseases using the L178 Mab because the clone was readily available at the time of the invention, and Seth and Galandrini disclose the CD44 Mabs as being inherently cytotoxic. To enhance or modify the method of treatment, one could readily have modified the antibody of Herrlich to create an antibody conjugate because Heider discloses anti-CD44 antibody conjugates for enzymes, toxins, and radioactive compounds being formulated with adjuvants, and Creekmore discloses antibody conjugates with hematogenous cells to improve cellular interactions. Accordingly, the claims were *prima facie* obvious at the time of the invention in view of the references.

14. Claims 33-35 are rejected under 35 U.S.C. 103(a) as being obvious over Linderhofer et al. (US 20020051780; published May 2, 2002; hereinafter referred to as "Linderhofer") in view of Hellstrom (USPN 5,980,896; published November 9, 1999; hereinafter referred to as "Hellstrom").

The interpretation of Claim 33 is discussed supra. Claims 34 and 35 are directed to antibodies conjugated to a cytotoxic moiety or a radioisotope.

The interpretation of Linderhofer is discussed supra. Linderhofer does not disclose antibodies conjugated to a cytotoxic moiety or a radioisotope.

Hellstrom discloses immunoconjugates (Col. 13, lines 1-9; i.e., antibody conjugates) comprising immunotoxins comprising cytotoxic agents (Col. 3, line 20-48; Col. 13, line 39-47) and radioisotopes (Col. 13, lines 48-54).

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the methods of Linderhofer to "extending survival and delaying disease progression" with anti-CD44 monoclonal antibodies because the antibodies were readily available at the time of the invention, and methods for modifying antibodies to formulate immunoconjugates were known in the art as taught by Hellstrom, and which immunoconjugates could further enhance the method effects.

Thus, the claims were obvious at the time of the invention in view of the reference disclosures.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 1-4 and 12-15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 23-26 of copending Application No. 10/647,818 (hereinafter referred to as "'818") in view of Queen et al. (5,530,101; published June 25, 1996; filed December 19, 1990; hereinafter referred to as "Queen").

See the interpretation of Claims 1-4 under sections 8 and 9, supra. Claims 12-15 are drawn to the method for treating a patient suffering from a cancerous disease comprising administering to the patient cytotoxic, anti-cancer antibodies encoded by the clone deposited with ATCC as PTA-4621 in a mixture with an adjuvant, and the antibodies are produced by a method (not claimed) wherein the antibodies are humanized and chimeric forms thereof, and/or conjugated to a toxin, enzyme, radioactive compound or hematogenous cell, and administering the antibody conjugate with a pharmaceutically acceptable adjuvant to mediate treatment.

Although the conflicting claims are not identical, they are not patentably distinct from each other. Each of the applications listed above recite a clone and antibody by deposit number (PTA-4621) and all of the antibodies were produced by the method recited in the instant application.

Claims 23-26 of the '818 application are drawn to processes for mediating cytotoxicity of a human tumor cell which expresses CD44 antigenic moiety on the cell surface comprising: contacting said human tumor cell with an isolated monoclonal antibody or antigen binding fragment thereof, said antibody or antigen binding fragment thereof being an isolated monoclonal antibody or antigen binding fragment thereof which binds to said expressed CD44 antigenic moiety, said antigenic moiety characterized as being bound by an antibody having the identifying characteristics of a monoclonal antibody encoded by a clone deposited with the ATCC as PTA-4621, whereby cell cytotoxicity occurs as a result of said binding, and with humanized and chimeric forms of the monoclonal antibody, and antibodies conjugated to enzymes, radioactive compounds, and hematogenous cells. Therefore, claims 23-26 in the "818 application anticipate the claims in the instant application because the claims are species of the generic claims 1-4 and 12-15 in the instant application.

In addition it would have been obvious to produce humanized, chimeric and conjugated antibodies in view of Queen, since the antibodies are for human therapy and this is routinely done for antibody immunotherapy in humans.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

16. No claims are allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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